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ONLINE EXCLUSIVE

Hormone therapy for menopausal symptoms: Putting benefits and risks into perspective

Too many patients have needlessly foregone the relief provided by hormone therapy; timing of treatment can make all the difference.

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PRACTICE RECOMMENDATIONS

- *After assessing an individual's benefit-risk profile, consider prescribing estrogen therapy (ET) or combined estrogen/progestin therapy (EPT) for management of vasomotor and vaginal symptoms of menopause (vaginal ET for local symptoms only).* (A)
- *Use the lowest effective doses of ET and EPT, as they may be better tolerated and have a more favorable benefit–risk ratio compared with standard doses.* (A)
- *Do not use hormone therapy for coronary protection* (A)*, although initiation by women ages 50 to 59 years or by those within 10 years of menopause may reduce cardiovascular risk.* (B)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Findings from the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study[1,2] have left physicians and patients confused about the risks and benefits of hormone therapy (HT) and have dramatically affected prescription patterns.[3] After the WHI trial findings were published in 2002,[1] use of HT declined dramatically; many women discontinued therapy or switched to lower doses, while others turned to alternate therapies.[4] This, despite long-standing evidence that HT administered as estrogen alone (ET; for hysterectomized women) or in combination with progestin (EPT; for nonhysterectomized women) effectively controls menopausal symptoms—hot flashes, vaginal atrophy, insomnia, and sexual problems.[5]

When interpreting results of recent clinical trials, it is important to consider how closely the trial subjects resemble patients in your practice. Patients in HT clinical studies may range from younger women who are newly menopausal to older women who experienced menopause decades ago. Women also have differing risk factors that determine whether HT is appropriate treatment.

Recent reanalyses of WHI data and other studies, as well as new guidelines from the North American Menopause Society (NAMS), have helped to clarify the benefit–risk profile of HT according to patient characteristics. This article places clinical trial evidence in perspective and explains how you can evaluate the benefit–risk profile of HT for individuals.

What are the benefits of HT?

The primary indication for HT is treatment of vasomotor symptoms, which are common at the time of menopause and can diminish quality of life.[5] The efficacy of HT in alleviating these symptoms is well established.[6] Hot flash rates

A meta-analysis found that hormone therapy's fracture prevention benefits were particularly marked in women younger than 60 years.

are highest in women during the first 2 years postmenopause,[7] and most women use HT for up to 2 years.[8] A study of women who had recently become postmenopausal (45-58 years of age) showed a significant reduction in vasomotor symptoms over 5 years with ET/EPT.[9]

Both oral and vaginal ET effectively relieve vaginal dryness.[5,10] A meta-analysis of 10 clinical trials showed that low-dose vaginal ET was as effective as systemic ET in providing relief of the signs and symptoms of urogenital atrophy.[11]

Nonhormonal treatments are also sometimes prescribed off label to treat vasomotor symptoms for women who cannot or choose not to use estrogens. Such agents include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, clonidine, and gabapentin.

A meta-analysis found that these treatments were more effective than placebo in reducing hot flashes in postmenopausal women, but the magnitude of symptom relief with these drugs has been less than that observed with estrogens.[12] In another study, off-label use of antidepressants greatly attenuated hot flashes for some patients.[13]

NAMS recommends that women with moderate-to-severe menopause-related hot flashes who have concerns with, or contraindications to, estrogen-containing treatments, consider other treatments, such as SSRIs or gabapentin;[7] however, high-quality studies evaluating these therapies in women with moderate-to-severe hot flashes are lacking.[12]

Phytoestrogens such as soy compounds and black cohosh may be helpful, although results have been variable in clinical trials.[14] Common adverse events associated with black cohosh treatment include gastrointestinal complaints and rashes. There have been rare reports of liver toxicity, suggesting the need for further investigation.[15]

Protecting bone mass density and reducing risk of fractures

Estrogen therapy. In the WHI study, ET reduced the rates of hip fractures (P=.01), clinical vertebral fractures (P=.02), and total osteoporotic fractures (P<.001).[16] The reduced risk was not affected by patient age.[17] The randomized Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study showed protection against early bone loss with ET vs placebo. After 2 years of follow-up, 55% of placebo-treated patients exhibited >2% loss of spine bone-mass density, compared with just 7% of women using ET (0.625 mg/d).[18]

Estrogen-progestin therapy. The WHI study[1,19] confirmed the reduced risk of osteoporotic fractures with EPT seen in previous clinical studies, and the Women's HOPE study[18] confirmed EPT's protective effect against bone loss. In a meta-analysis of HT studies (most of which used EPT), the benefits associated with HT in fracture prevention were particularly marked in women younger than 60 years,[20] although no effect of age or time since menopause was observed in the WHI study.[19] Initiation of EPT soon after menopause has been shown to improve postural balance to levels seen in premenopausal women, which may contribute to protection against fracture.[21]

Nonhormonal therapy for bone health. For women who are not candidates for HT, therapeutic options for maintaining bone health include bisphosphonates, raloxifene, teriparatide, and calcitonin.[22] In addition to calcium and vitamin D supplementation, the NAMS guidelines recommend bisphosphonates as first-line treatment, followed by raloxifene, for postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis who are at greater risk of spine fracture than hip fracture.[23] Teriparatide is generally reserved for women at high risk of fracture.[23] Calcitonin, typically administered as a nasal spray, is approved for osteoporosis treatment, but not prevention. It is generally considered an alternative for patients who cannot tolerate other therapies.[23] Denosumab, a monoclonal antibody, is a new drug indicated in women at high risk for fracture or who cannot tolerate other therapies.

What are the potential risks of HT?

Risk factors associated with HT relate to a woman's baseline disease risks: age; age at menopause; cause of menopause; time elapsed since menopause; prior use of any hormone; types, routes of administration,

and doses of HT used; and medical conditions emerging during treatment.[5] When assessing the benefit–risk profile of HT for any patient, take into account the woman's health profile as well as the chance of harm associated with any particular therapy.

Cardiovascular disease: Timing of HT matters

Estrogen therapy. Although observational studies,[24,25] such as the Nurses' Health Study, suggest a reduced risk of cardiovascular events with ET, randomized clinical trials[16,26] have shown either no effect or increased risk of cardiovascular disease among women using ET. In the ET arm of the WHI study,[16,26,27] there was an increased risk of stroke and a trend toward increased risk of peripheral arterial disease, but no effect on the incidence of coronary heart disease (including myocardial infarction and coronary death).

The disparity between observational and randomized clinical trial results is now believed to be a result of differences in patient characteristics (particularly age) and timing of initiation of HT in both types of studies.[5] Demographic or biologic differences influence the effects of HT on cardiovascular risk. This timing hypothesis is supported by data from an observational study,[28] meta-analysis of clinical trials,[29] secondary analyses from the WHI,[30] and a substudy of the WHI (WHI-Coronary Artery Calcium Study).[31]

Estrogen-progestin therapy. As with ET, observational studies[24,25] have indicated a reduced risk of cardiovascular events with EPT, whereas randomized clinical trials[1,26,32] have shown either no effect or increased risk of cardiovascular disease in women using EPT. A recent observational study of women taking primarily EPT (87%; 13% on ET) for a mean duration of 8.3 years found no significant difference in the risk of cardiovascular disease between groups exposed to HT and those unexposed (relative risk, 0.84; 95% confidence interval [CI], 0.16-4.13).[33]

The WHI study demonstrated an increase in cardiovascular event risk with EPT, particularly during the first year of treatment.[1] However, when results were adjusted for age and time since menopause, this risk was isolated to women ≥20 years past menopause, contrasting with a trend toward reduced risk of coronary heart disease in women who initiated HT within 10 years of menopause.[30]

In the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM), there was a significant increase in the number of major cardiovascular events with EPT vs placebo.[32] However, as in the original WHI study, most women in the WISDOM study were age 65 or older and thus did not fall into the younger age category that experiences cardiovascular benefit from HT.

Influence of age on cardiovascular risk. In the WHI and WISDOM studies,[1,16,32] women tended to be at least 10 years postmenopause, whereas the observational studies included younger women who started HT sooner after menopause. The WHI data have shown no increased risk of cardiovascular disease with ET overall and have shown lower coronary artery disease risk in women ages 50 to 59 years.[26] There was also a trend for reduced cardiovascular risk with EPT among women who were up to 10 years postmenopause.[30]

In a meta-analysis[34] of randomized studies, there was a reduction in the risk of cardiovascular events with HT in women younger than 60 years, but an increased risk of events during the first year of treatment in older women. HT has been associated with reduced blood pressure in women who are <5 years postmenopause but not in women ≥5 years postmenopause.[35] Thus, the data appear to support the hypothesis of a "therapeutic window" during which ET or EPT may be cardioprotective in younger, newly menopausal women, and an increased risk for cardiovascular disease with EPT, principally confined to older women at an increased distance from menopause.

Increased risk for cardiovascular disease with EPT is seen mostly in older women years after the onset of menopause.

Thromboembolism: Patient age makes a difference

Estrogen therapy. Observational data from the UK General Practice Research Database, which included women ages 55 to 79 years, demonstrated a reduced risk of deep vein thrombosis (P=.008) and a trend toward reduced risk of venous thromboembolism (VTE; P=.057) among users of ET.[36] However, the ET arm of the WHI showed an early increased risk of venous thrombosis,

For otherwise healthy newly menopausal women age <60 years, the risk of thromboembolism from ET or EPT is negligible.

particularly within the first 2 years of use.[37] The absolute incidence of VTE (including deep vein thrombosis and pulmonary embolism) was relatively low in the study, and risk of pulmonary embolism alone was not significantly different from that seen with placebo; however, the use of conjugated estrogens did increase the relative risk of VTE in postmenopausal women without a uterus. Risk also increased with obesity.[37]

Estrogen-progestin therapy. The WHI study demonstrated an increased risk of VTE with EPT compared with placebo, the risk increasing with advancing age and obesity.[38] In addition, the risk of VTE was significantly greater with EPT than with ET in the same study.[37] In women younger than 60 years, the projected 5-year risk associated with EPT was 1.4% in obese women, compared with less than 0.5% in women of normal weight. In the WISDOM study, which involved women older than 65 years, there was a significant increase in VTE incidence with EPT vs placebo (hazard ratio [HR], 7.36; 95% CI, 2.20-24.60).[32]

Thrombotic risk in perspective. The risk of VTE is an important determinant of the benefit–risk profile when prescribing HT. Data from observational and randomized trials have shown an increased risk of VTE with oral HT.[5,39] In women with preexisting cardiovascular disease, the use of statins appeared to negate the increased risk of thromboembolism with EPT.[40] In the WHI trials, the absolute VTE risk associated with either EPT (7 per 10,000 women per year of use) or ET (4 per 10,000 women per year of use) in women younger than 60 years was lower than in older women[37]—and considered rare by NAMS consensus. Thus, for otherwise healthy newly menopausal women younger than 60 years, carefully consider the benefits of ET or EPT against the negligible risk of thromboembolism.

Limited observational data suggest lower risks of VTE with transdermal ET compared with oral ET,[41] but there is no conclusive evidence from randomized controlled trials on this subject.[5] Low-dose oral and transdermal formulations may provide promising routes of administration, pending further studies. Evidence suggests that women with a history of VTE or women who have factor V Leiden are at increased risk for VTE with HT use.[39] Use caution, therefore, when considering HT in women at higher risk of VTE, such as those with prior VTE or thrombogenic mutations, those undergoing surgery, or those who are immobilized.[39]

Breast cancer: Risk with ET may be dose related

Estrogen therapy. Observational studies have suggested an increased incidence of breast cancer among women using ET for more than 1 year, with the risk increasing as use continues.[36,42] In contrast, results of the WHI study showed that invasive breast cancer was diagnosed at a 23% lower rate in the ET group than in the placebo group, although this difference did not reach statistical significance (P=.06).[16] The Women's Health Study showed no association between current use of ET and the risk of total breast cancer or invasive breast cancer.[43] The degree of breast cancer risk may depend on dose, as a meta-analysis of studies showed no increase in breast cancer risk with use of ET at ≤0.625 mg/d.[44] In addition, the incidence of breast cancer has been shown to be lower in women who do not have benign breast disease or first-degree relatives with breast cancer.[45]

Estrogen-progestin therapy. Observational studies have shown an increased risk of breast cancer with EPT.[42,46] In the WHI study, there was a significantly increased relative risk of invasive breast cancer in women receiving EPT over a follow-up of 5.6 years (HR, 1.24; 95% CI, 1.02-1.50).[47] However, some have noted that the observed increase in the incidence of invasive breast cancer in the EPT arm vs placebo was not statistically significant and could have resulted from chance alone.[48] A recent analysis of breast cancer incidence in the United States found a sharp decrease from 2002 to 2003,[49] suggesting that breast cancer risk diminished soon after discontinuation of EPT for many women following the publication of the WHI results.

A newly published WHI follow-up study has yielded similar findings regarding the incidence of invasive breast cancer with EPT. The small increase in cancer incidence compared with placebo was associated with positive nodes and the death rate in this group was also higher (2.6 deaths vs 1.3 per 10,000 women).

TABLE

Select hormone therapy according to nature and severity of symptoms[5,10,23]

Symptoms	Severity	Treatment
2 hot flashes per day	Mild	Exercise Diet Environmental temperature regulation
5-7 hot flashes per day Nighttime awakenings Night sweats/insomnia	Moderate-to-severe	HT for appropriate patients
Vaginal symptoms only (atrophic vaginitis)	Moderate-to-severe	Vaginal estrogen therapy
Osteoporosis	Established reduction in bone mass	Calcium + vitamin D plus bisphosphonate or raloxifene or extended HT for appropriate patients when preceding therapies are not tolerated or not appropriate
Optimal candidates for HT: • recently menopausal (<10 years) • <60 years of age • no risk factors for cardiovascular disease or breast cancer.		

HT, hormone therapy.

These findings do not apply to ET alone.[50]

Breast cancer risk in perspective. When interpreting increased risk, consider the absolute risk. In the WHI study, the absolute risk of invasive breast cancer increased by 4 to 6 cases per 10,000 women per year in the EPT group vs placebo.[47] Similarly, a systematic review of clinical studies showed that EPT was associated with an increase of 4 breast cancer cases per 10,000 women per year.[51] The increased risk of breast cancer with combined EPT is similar to that associated with early menarche or late menopause and is smaller than that associated with nulliparity or having children after 30 years of age.[52]

Assessing risks and benefits for the potential HT patient

The first step in treating patients who have hot flashes is to determine the extent of their symptoms and the effect on their quality of life (**TABLE**).[5,10,23] Two hot flashes a day is considered mild and will usually respond to lifestyle measures such as exercising, avoiding alcohol and spicy foods, and staying in a cool environment. If the patient wakes in the night with hot flashes and night sweats that lead to insomnia, this may be more serious and require treatment. Consider HT for moderate-to-severe hot flashes—ie, 5 to 7 a day. HT is the only pharmacologic therapy indicated for the treatment of hot flashes.

Although professional guidelines recommend appropriate use of HT, publication of the WHI study caused many patients to mistrust and fear hormonal approaches to managing menopausal symptoms.[3,4,53] Among those who discontinued HT, many have had vasomotor symptoms recur, and some patients remain untreated.[53] A thorough discussion of individual needs and risk factors can help assess whether a patient is a suitable candidate for HT, and patient education and counseling may help alleviate concerns.[54]

When considering HT for a patient, take into account risk factors, such as baseline disease, age at menopause, cause of menopause, prior hormone use, variations in HT used, and age and time elapsed since menopause.[5] An individual's risks for cardiovascular disease, breast cancer, and osteoporotic fractures will

A meta-analysis of studies showed no increase in breast cancer risk from estrogen therapy given at a daily dose of up to 0.625 mg.

help determine the most appropriate treatment.[55] In the WHI, symptomatic women who were younger and closer to the menopausal transition experienced the greatest relief of vasomotor symptoms with EPT and were less likely to experience adverse effects compared with older women.[56] The WHI data also showed that the prevalence of menopausal symptoms decreased with increasing age, occurring most commonly in women ages 50 to 54 years.[56] The WHI findings have been shown to apply to HT regimens in general.[57]

Specific recommendations. Current prescribing guidelines[5] recommend using ET/EPT to treat moderate-to-severe vasomotor symptoms associated with menopause when the benefits of short-term therapy outweigh the risks. For women who experience mainly vaginal symptoms rather than vasomotor symptoms, vaginal ET is recommended.

HT is not recommended for coronary protection in women of any age, as there is evidence that use in older women increases the risk of cardiovascular events.[5] However, HT does not appear to increase the risk of CV events if initiated by women ages 50 to 59 years or by those within 10 years of menopause. There is evidence of an increased risk of VTE with oral HT, although absolute risk is low in women ages 50 to 59 years.[5]

To prevent further bone loss and reduce the risk of osteoporotic fracture in women with established reduction in bone mass, the guidelines recommend extended use of HT, regardless of menopausal symptoms, when alternate therapies are not appropriate or cause side effects or when the safety and hazards of extended use of alternate therapies are not well established.[5]

Breast cancer risk increases with EPT use beyond 3 to 5 years, although the absolute risk is still considered rare.[5] Clinical evidence, including findings from the WHI study[16] and the Women's Health Study,[43] shows no increase in the risk of breast cancer in women receiving ET. Further, the risk of breast cancer with ET may be lower in certain subgroups of women, such as those with lower Gail risk estimates based on age, history of benign breast disease, age of menarche, age of first birth, race/ethnicity, and mothers and sisters with breast cancer;[58] women with no first-degree relatives with breast cancer; women without benign breast disease; and women with no prior hormone use.[45]

Initiating HT for symptom control in newly menopausal women may provide additional benefits, such as reduced osteoporosis and cardiovascular risk, that outweigh the small risks associated with HT in this younger age group.

Evaluate the relative risks vs benefits, and use the lowest effective dose. Evaluate older women in a similar fashion. Those who continue to experience symptoms after discontinuing HT can be restarted on low-dose HT if symptoms do not abate. JFP

Hormone therapy is not recommended for coronary protection in women of any age.

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